



Atty. Dkt. No.: P70463US0
Serial No.: 10/529,555
Declaration of Madsen

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Flemming MADSEN et al. Confirmation No.: 7874
Serial No.: 10/529,555 Group Art Unit: 1711
Filing Date: March 29, 2005 Examiner: Susan W. Berman
For: A HYDROGEL

DECLARATION OF FLEMMING MADSEN

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Flemming Madsen, do hereby declare the following:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-captioned application. I reside in Højagervej 15B, DK-2942 Skodsborg, Denmark, and I am currently employed by Coloplast A/S which is also located at Høltedam 3, DK-3050 Humlebæk.
2. My educational background is set forth on my Curriculum Vitae (CV) attached hereto as Attachment A. As indicated, I have a Master's Degree and Doctorate from the Danish University of Pharmaceutical Sciences.

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3. My professional experience, which is also set forth on the attached CV, Attachment A, includes over 13 years of experience in the pharmaceutical sciences field, with at least 10 years experience specifically in the area of formulations, hydrogels and polymers. As a result of my education and experience, my professional contemporaries and colleagues consider me an expert in the hydrogel and polymer field.
4. Based upon my education and experience, I have an opinion regarding what the level of ordinary skill in the medical and wound care field generally would be. Persons of ordinary skill in this art would include those individuals having attained Bachelors or Masters degree in chemistry, physics, pharmaceutical science or biology or at least 3-5 years of experience in developing and testing hydrogel polymer containing wound and medical care products.
5. Drawing upon my expertise in this industry, I understand the level of ordinary skill in the art at the time the above-captioned application was originally filed (October 2002) and can offer my expert opinion as to how persons of ordinary skill in

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6. I have read and understand the Office Action of November 14, 2007, in connection with the above-captioned application.
7. The Examiner rejected claims 15 and 16 under 35 U.S.C. §112, second paragraph, as being indefinite because the Examiner considers the term "and copolymers or blends of the foregoing" is not clear.
8. The specification at page 16, lines 19-24, identifies a number of hydrophilic saturated polymer species which could be used in the hydrogel of Applicants' claimed invention. These species of polymers also include copolymers, comprising one or more of these polymer species identified. In my expert opinion, one of ordinary skill in the hydrogel polymer or wound care arts, could read the language of claims 15 and 16, in view of the instant specification, and understand the metes and bounds of the claims intended scope with regard to what polymers are intended to be covered by the claims. As such, I believe that the claim language of claims 15 and 16 are sufficiently definite under 35 U.S.C. §112, second paragraph.

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9. The Examiner rejected claims 11-23 as obvious over U.S. Patent Application 2001/0044482 to Hu et al., in view of USP 5,844,016 to Sawhney et al. The Examiner asserts that Hu et al. disclose all of the elements of the claimed composition, except for the use of a water soluble peroxydisulphate photoinitiator, which is disclosed by Sawhney et al. Therefore, according to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to combine the compositions of the Hu et al. and Sawhney et al. references, to arrive at Applicants' claimed invention.
10. I have read and understand Hu et al. Hu et al. disclose an interpenetrating polymer network hydrogel composition suitable for use in a contact lens. Hu et al. provide an example (Example 3, paragraphs 0085-0087) of a PVP/PEG-DMA containing system for contact lenses. Here, the sample was exposed to UV irradiation for 5 minutes and then thermally cured for one or more hours to obtain a contact lens (usually a thickness 30-100 um). I note however, that in each example in Hu et al., the polymer solution is degassed, meaning that the photoinitiator in Hu et al. is sensitive to the presence of oxygen in the solution, and therefore cannot be a peroxydisulphate compound.

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11. I have read and understand Sawhney et al. Sawhney et al. teach hydrogel polymers used as tissue glues in surgical applications. The specification teaches that the preferred photoinitiator is Eosin Y, because it absorbs strongly to most tissue and is an efficient photoinitiator (col. 6, lines 30-33). Sawhney teaches that thermal initiators, also described as redox initiators, such as potassium persulfate and ammonium persulfate can be used at 37°C (col. 6, lines 38-44). After a thorough reading of Sawhney et al., I could find only one example (Example 19) where potassium persulfate is used (0.02 g). In Example 19, Sawhney et al. compare different oxidant solutions in a redox initiated polymerization, not a UV initiated photopolymerization. Furthermore, a comparison of Applicants' claimed invention, and Example 19 shows that Sawhney et al. use potassium persulfate at a higher concentration (2% by weight) than Applicants'. Sawhney et al. also teach that the persulfate initiated gel does not adhere to tissue as well as the eosin initiator gel.
12. On column 13 of their patent, Sawhney et al. show UV-polymerizations times of 40 seconds for 0.5 ml of PEG based biodegradable polymer solutions using a different photoinitiator in their Example 1. In Example 19 of Sawhney et al., potassium persulfate is used as a thermal or Redox initiator reference, but

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not as a photoinitiator. The concentration of persulfate in this example (0.02 g persulphate/ml monomer solution) is approximately twice the amount that Applicants use for UV-polymerization.

13. In my expert opinion, one of ordinary skill in the hydrogel polymer or wound care arts, would understand that Sawhney et al. do not teach or suggest that peroxydisulphates can be used as a photoinitiator for saturated hydrophilic polymers. Sawhney et al. merely teach that peroxides can be used as thermal redox based initiators, which was already known in the art.
14. The problem to be solved by Applicants was to find a way to lessen the time it took to prepare and completely cure cross-linked water-soluble hydrogel sheets or coatings, up to 2 cm thick, in a simple and non-toxic manner.
15. As I stated above, Hu et al. teach water-soluble hydrogels used for contact lenses. Sawhney et al. teach a surgical sealant or glue. Both lenses and sealants, in my experience, generally have a thickness between about 30 μm to 100 μm . Polymerization times in such thin sheets are not usually a significant problem. As such, in my expert opinion, one of ordinary skill in the art,

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would not have considered Hu et al. when attempting to solve Applicants' problem.

16. Even if one of ordinary skill were to start with the polymer hydrogels of Hu et al., it is my opinion the solution to Applicants' problem would not have been found by considering the teachings of Sawhney et al. for the following reasons. First, Sawhney et al. teach tissue glues and sealants used in surgical applications. It would have been understood that these sealants would have been extremely thin (30 μm - 200 μm thick). As I stated with regard to Hu et al., polymerization times in such thin sheets are not usually a significant problem.
17. Moreover, one of ordinary skill, when reading Sawhney et al., would not have found any teaching or suggestion to use peroxydisulphate compounds to photoinitiate the curing of the hydrogels, because Sawhney et al. teach the use eosin Y or Igracure as photoinitiators. As such, it is my expert opinion that those of ordinary skill in the hydrogel polymer art would not have had any motivation to try to use peroxydisulphate compounds taught in Sawhney et al. to photoinitiate the curing of water-soluble polymer hydrogels, and would not have had any reasonable expectation of success to do so.

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18. In the Office Action, the Examiner combines the Hu et al. and Sawhney et al. references by including Applicants' statements in the Background section of the present application, which teach that peroxides in general were known in the art as photoinitiators of vinyl polymerization. The Examiner then combines Applicants' statements with the teachings of Hu et al. and Sawhney et al., and argues that one of ordinary skill in the art, at the time the invention was made, would have been motivated to combine Hu et al. in view of Sawhney et al. and in view of the prior art knowledge of photoinitiators, as discussed by Applicants, to arrive at Applicants' invention. I disagree with the Examiner's reasoning.

19. The point of Applicants' Background discussion of vinyl polymerization is to show that the use of peroxides and persulphates on non-water soluble, unsaturated vinyl monomers and polymers had been known. However, these photoinitiators had never been used on hydrophilic water-soluble polymers as taught in Applicants' claimed invention. In other words, the art teaches away from the combination. Therefore, in my opinion, one of ordinary skill would not have combined the teachings of Hu et al. and Sawhney et al. with what was known in the art to arrive at

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Applicants' claimed invention.

20. My expert opinion is further supported by two recent articles by Ikkai and Adachi:

(1) Fumiyoshi Ikkai and Eiki Adachi, *Novel Method of Producing Polymer Gels in Aqueous Solution Using UV Irradiation*, *Macromolecular Rapid Communications*, Volume 25, Issue 16, Date: August 26, 2004, Pages: 1514-1517; and

(2) Fumiyoshi Ikkai and Eiki Adachi, *Mechanism of UV-Induced Gelation of Acryloyl-Type Monomer and Polymer Solutions Using Persulfate as Photoinitiator*, *Macromolecular Chemistry and Physics*, Volume: 208, Issue: 3, Date: February 5, 2007, Pages: 271-276

21. In reference (1), Ikkai and Adachi claim to have developed a novel method of producing polymer gels using UV irradiation. Their method involves the use of a persulfate, such as ammonium, potassium, or sodium persulfate as a UV photoinitiator. They claim their method solves the problems associated with the previous techniques and enables one to produce polymer gels more easily. According to the authors, their paper contains the first

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reported UV-induced gelation method using persulfate as a photoinitiator. They are seemingly unaware of our published patent application, but the essence is that their work in (1) and (2) supports both our claims and the suggested mechanism. The authors make the following statements:

Most other UV photoinitiators used are not water-soluble because of aromatic groups in the molecule, which makes them hardly appropriate for water-soluble systems.

Most UV photoinitiators can only be used for solutions whose thickness is less than a few hundred micrometers.

22. The efficiency of the UV-induced gelation method was verified by Ikkai and Adachi for more than twenty kinds of monomers having various types of side-chain structure. The authors show the method to be applicable to both acryloyl-type monomers and polymers, which are similar in chemical properties to those claimed in the present invention.

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23. Ikkai and Adachi demonstrate in (1) a relationship between concentration of persulfate and curing time, which is further elaborated in (2). They state the UV-induced gelation time is inversely proportional to the square root of the level of persulfate, i.e., UV-photoinitiator, indicating that gelation progresses according to a radical polymerization process.
24. In one example in (2) Ikkai and Adachi use a test tube of 8 mm, which is comparable to the 5 mm gel thickness we use in our examples. In their case the fastest gelation they obtain set in between 2-5 minutes using a persulfate concentration of 0.05 M. There is no information on the gel strength of these hydrogels.
25. In contrast, Example 1 (p.24) of Applicants' present application discloses a persulfate concentration of 0.04M to cure a 5 mm gel in approximately 1 minute. Applicants' more recent studies suggest that Applicants can obtain approximately the same curing time, and with slightly less gel-strength, even when the persulfate concentration is lowered to 0.008 M. See paragraph 27 detailing Applicants' recent experimental data.
26. Therefore, in my expert opinion, in general, it can be stated that the time for gelation/curing of a hydrogel, according to the

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claimed composition of the present application, is directly related to the thickness of the hydrogel, and may vary from seconds to minutes (p.15). Hence, total curing could be obtained within seconds for hydrogel of 30 μm in thickness, whereas a gel of 1 cm in thickness would require a few minutes to be completely cured.

Experiment with 0.2% persulfate ($8.4 \times 10\text{M}^{-3}$)

27. 20 g of polyvinyl-pyrrolidone (PVP K90) was mixed with 4 g of polyethylene-glycol dimethacrylat 1000 (PEG-DMA 1000) and 0,2 g natriumperoxidisulfate in 75 g of 0.1 M citric acid/citrate buffer pH 6.0. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: 200 W/cm, microwave powered "D"-spectral type lamp with a conveyor speed of 0.2 m/min). A sheet hydrogel of 5 mm thickness was obtained.
28. The rheological properties of the gel was examined using dynamic oscillation rheology determining the viscoelastic moduli, G' (Elastic modulus) and G'' (Loss modulus) and tan delta (G''/G') at a frequency of 1 Hz, 25°C. The viscoelastic moduli of this hydrogel was $G' = 3443 \text{ Pa}$, $G'' = 1290 \text{ Pa}$ and tan delta = 0.375

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29. The above experiment describes the preparation of a basic hydrogel of the invention with photoinitiator (persulfate) concentration approximately 5 times less than the standard formulation given in example 1 in patent application. The gel strength is slightly lower compared to the standard recipe, but is fully cured after 1.5 - 2 minutes.

Experiment with increased thickness: A sheet of 2.0 cm

30. 20 g of polyvinyl-pyrrolidone (PVP K90) was mixed with 4 g of polyethylene-glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 75 g of 0.1 M citric acid/citrate buffer pH 6.0. The polymer solution was dispensed into a suitable mold in 2,0 cm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp through 3 cycles (specifications: 200 W/cm, microwave powered "D"-spectral type lamp with a conveyor speed of 0.1 m/min). A sheet hydrogel of 2.0 cm thickness was obtained.
31. The rheological properties of the gel were examined using dynamic oscillation rheology determining the viscoelastic moduli, G' (Elastic modulus) and G'' (Loss modulus) and tan delta (G''/G') at

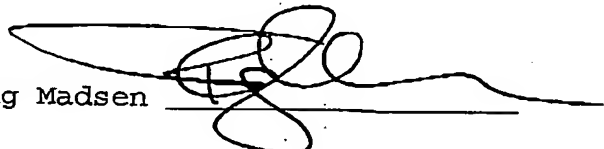
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a frequency of 1 Hz, 25°C. The viscoelastic moduli of this hydrogel was $G' = 2733$ Pa, $G'' = 1140$ Pa and $\tan \delta = 0.417$

32. The above experiment describes the preparation of a basic hydrogel of the invention with a thickness considered to be the upper limit of thickness range. The gel strength is slightly lower compared to the standard recipe, and full curing time is 4-5 minutes.

33. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 13-5-2008

Flemming Madsen 

Attachment A: CV of Flemming Madsen

Attachment B: Ikkai and Adachi references (1) and (2)

CURRICULUM VITAE
Flemming Madsen

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Career 2007- : Head of Medical Delivery Systems, Coloplast Incubation,
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 2000- 2007 : *Senior Scientist & Project Manager*, Coloplast
Research, Coloplast A/S
1999–2000 : *Associate Professor*, Department of Analytical and
Pharmaceutical Chemistry, The Danish University of Pharmaceutical
Sciences.
1998-1999: *Research Associate Professor*, Department of Analytical
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1995–1998 : *Assistant Professor*, Department of Analytical and
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Sciences.
1992–1995 : *Ph.D.-studium*, Department of Analytical and
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1990–1992 : *Research and Teaching Assistant*, Department of
Analytical and Pharmaceutical Chemistry, The Danish University of
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Research stay 1997-1998: *Visiting scientist*, Biomedical and Drug Delivery
Laboratories, Dep. of Chemical Engineering, Purdue University, IN,
USA
1993-1994: *Visiting scientist*, School of Pharmacy, Biomedical and
Physical Sciences, University of Portsmouth, UK

Supplementary education *Coloplast E-MBA programme, Henley Management College*
Aug. 2006-
Executive Certificate in Management, Henley Management College,
July 2007
CMP- Coloplast Managing Programme, January 2007
CBP- Coloplast Business Programme., September 2005
EU-GMP Guidelines – Interpretation and Application –
(With examination) , Pharmakon, oktober 2003

Coaching, February 2003
Analytical Challenges in the Formulation Design of Pharmaceutical Proteins, The Danish University of Pharmaceutical Sciences, November-December 2002
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Publications

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Birdi, K. S., Madsen, F. and Eberth, K. : Determination of van der Waals forces in monolayer films of lipids & biopolymers. *Equation of state for two-dimensional films*, *Colloid & Polymer Science* 272 (1994), 1000-1004.

Latest abstracts

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Madsen, H.B., Rozlosnik N., Manniche, S., Madsen, F., Nielsen, H.M & Ifversen P, Mechanistic studies on functional delivery of

nanoparticles to the epidermis, Pharmaceutical Science World Congress, Amsterdam, 2007

Nielsen, A. L., Madsen, F., Larsen, K. L., Controlled release of ibuprofen from cyclodextrin modified hydrogels, PharmSciFair Nice, June 2005.

Woldum, H. S., Madsen, F., Larsen, K. L., Cyclodextrin assisted release of poorly water-soluble drugs from hydrogels, PharmSciFair Nice, June 2005.

Kirkby, N., Heydenreich, A. H., Iversen, P., Madsen, F., Samuelsen, P., Verland S. and Dalsgaard K., Efficient transcutaneous immunization using ISCOM-based formulations, IMV Immunopotentiators in modern vaccines; Malaga, Spain May 2005

Other publications

Madsen, H.B., Iversen P., Madsen, F., Manniche, S. & Nielsen, H.M., Farvel til sprøjten: Udvikling af vaccineplaster med nanopartikler, Lægemedelforskning, Faculty of Pharmaceutical Sciences, University of Copenhagen, 2007

**Ph.D-supervision/
Censorship**

Supervision: M. Qvist : Chemical Permeation Enhancers i Transdermal Drug Delivery Systems. 1998-2001.

Censorship:

Karsten Petterson, "Combined formulations based on prodrugs and in situ gelling systems. Design and pharmaceutical chemical characterization", May 2004.

Appointment Committee Member for Associate Professorship at FARMA-KU, 2006 and 2007.

Miscellaneous

Several *peer reviews* for Biomaterials, Int. J. Pharm, J. Control. Rel. and Eur. J. Biopharm Sci.

Member of Committee of the CRS Jorge Heller Journal of Controlled Release Outstanding Paper Award, 2001- 2005.

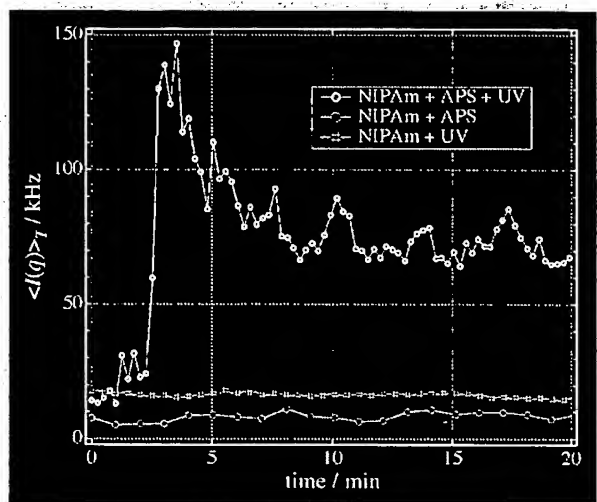
2003 AAPS PharmSci Manuscript Award as Co-Author of :

Qvist, M. H., Hoeck, U., Kreilgaard, B., Madsen, F. and Frokjaer, S., Application of confocal laser scanning microscopy in characterization of chemical enhancers from drug-in-adhesive transdermal patches, AAPS Pharm Sci., 4 (1) (2002): article 3.

Memberships: *Protein Formulation Network*, The Danish University of Pharmaceutical Sciences; *Biopharmaceutical Section*, The Danish Pharmaceutical Society, *Controlled Release Society*

Summary: We developed a novel method of producing polymer gels in aqueous solution using UV irradiation. Persulfates were effective photosensitive initiators of polymerization and/or gelation of acryloyl-type monomers/polymers. The gelation was confirmed by an abrupt increase in light scattering intensity, $\langle I(q) \rangle_T$, at the gelation point. The gelation method entails significant advantages: it does not need any cross-linkers, temperature control (heating), and additives except the persulfate.

The UV irradiation time dependence of light scattering intensity, $\langle I(q) \rangle_T$, for pre-gel solutions containing *N*-isopropylacrylamide (NIPAm) and/or ammonium persulfate (APS).



Novel Method of Producing Polymer Gels in Aqueous Solution Using UV Irradiation

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Received: May 13, 2004; Revised: June 22, 2004; Accepted: June 23, 2004; DOI: 10.1002/marc.200400196

Keywords: gelation; initiators; *N*-isopropyl acrylamide; light scattering; UV irradiation

Introduction

Various methods of producing polymer gels have been studied for many decades mainly from an industrial viewpoint.^[1–3] Most reported methods for gelation of aqueous monomer/polymer solutions involved either redox^[2–7] or thermal radical polymerization.^[2,3,8–11] When redox radical polymerization is used, the gelation of monomer solution is triggered by a redox initiator in the presence of a reaction accelerator. Usually, the gel-forming reaction starts when the accelerator is added to the pre-gel solution containing monomers, cross-linkers, and initiator. The monomers then react with the cross-linkers to produce gel networks. So, the additive must be put in contact with the solution by injecting it at the time to start. If the pre-gel solution has an interface sensitive to physical stimuli or is in a closed space, this method is not achievable. On the other hand, thermal radical polymerization requires heating the reaction bath above approximately 50 °C in order to activate radicals without adding a reaction accelerator. So, this

method is unsuitable for the preparation of heat-sensitive polymer gels, such as *N*-isopropyl acrylamide (NIPAm) gels. Indeed, though often employed for producing nanogel particles in emulsions, the thermal gelation method is hardly used to obtain gels having a macroscopic size. Other gelation methods include photopolymerization,^[2,3] where active radicals are generated through UV irradiation,^[2,3,12–18] high-energy electron beam,^[19–21] or γ -ray irradiation.^[22–24] The photopolymerization methods are very effective to avoid both the above-described contact issue and the heating problem. However, the high-energy electron beam and γ -ray irradiation require tricky measures for safe handling, which are not convenient for daily experiments on a laboratory or small factory scale. As a result, using UV irradiation is most convenient as a gelation method. However, most of the UV photoinitiators are not water-soluble because of aromatic groups in the molecule, which makes them hardly appropriate for water-soluble systems. Furthermore, most of them can only be used for solutions whose thickness is less than a few hundred micrometers.

Here we report on a novel method of producing polymer gels using UV irradiation. The method solves the problems associated with the previous techniques and enables one to produce polymer gels more easily.^[25] It involves the use of a persulfate, such as ammonium, potassium, or sodium persulfate as a UV photoinitiator. To our knowledge, this is the first reported UV-induced gelation method using persulfate as a photoinitiator. It has an edge over the other gelation methods because of the following points: (1) No cross-linker is necessary, that is, the polymer gel obtained consists of a single kind of monomer. (2) No temperature control is required. (3) No additives, such as a reaction accelerator or pH-adjustment agent, are required. (4) The photoinitiator used is transparent and nontoxic. The efficiency of the UV-induced gelation method was verified for more than twenty kinds of monomers having various types of side-chain structure. As discussed later, the method is applicable to acryloyl-type monomers and polymers.

Experimental Part

Samples

Acrylic acid, acrylamide, *N*-isopropyl acrylamide, methacrylic acid, methacrylamide, sodium *p*-styrene sulfonate, 2-(dimethylamino)ethyl acrylate, *N,N*-dimethyl acrylamide, 4-acryloyl morpholine, 2-hydroxyethyl acrylate, and ammonium persulfate were purchased from Wako Chemical Co. Ltd., Tokyo. *N*-Vinyl formamide, *N*-vinyl acetamide, vinyl acetic acid, 2-acrylamido glycolic acid monohydrate, mono-2-(acryloyloxy) ethylsuccinate, 2-acrylamido-2-methylpropane-sulfonic acid, polyacrylamide ($n = 10\,000$), poly(acrylic acid) ($n = 100\,000$), [2-(acryloyloxy)ethyl] trimethylammonium chloride, (3-acrylamidopropyl) trimethylammonium chloride, and [2-(acryloyloxy)ethyl]trimethylammonium methylsulfate were from Aldrich. 1-Vinyl imidazole was from Tokyo Kasei Kogyo co., Ltd.

UV Irradiation

UV irradiation was performed using a 500 W Deep-UV lamp (USHIO Inc., Tokyo, Japan) with an illuminance spectrum at $\lambda \leq 300$. Ammonium persulfate (APS) was used as a UV photoinitiator. Figure 1 shows the APS concentration (C_{APS}) dependence of the UV absorbance of APS aqueous solutions. The UV absorption spectrum was measured using a Jasco Model V-550 UV/VIS spectrophotometer (Japan Spectroscopic Co., Tokyo, Japan) with 1 cm path length at 20 °C in the range $190 \leq \lambda \leq 300$ nm. From Figure 1, the APS spectrum reveals a strong absorption peak around 190–220 nm, which is dependant upon the C_{APS} , indicating that APS molecules interact with each other. Hence we presumed that APS would act as an effective photoinitiator. It should be noted that the other persulfates, that is, potassium and sodium, have almost the same UV absorption spectra as APS.

Light Scattering (LS) Measurement

Gelation and/or polymerization was verified by "scattered light intensity monitoring". It is known that gelation can be

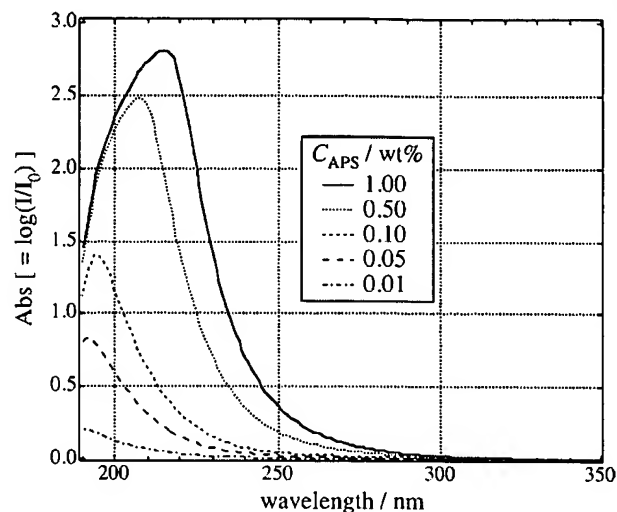


Figure 1. C_{APS} dependence of the UV absorbance spectrum of aqueous APS solutions.

detected by a dramatic increase in the scattered light intensity, $\langle I(q) \rangle_T$, with large fluctuations.^[4,8] The measurement of $\langle I(q) \rangle_T$ was carried out on a DLS/SLS-5000 (ALV, Co. Ltd., Langen, Germany) with a 22 mW He/Ne laser ($\lambda = 632.8$ nm). When irradiating a sample in the quartz test-tube with UV light in the opposite direction of the incidence of the He/Ne laser, $\langle I(q) \rangle_T$ was detected at 90°. The temperature of the sample was controlled by thermostatic water circulation. Since the original light from the UV lamp included some wavelengths as high as those emitted by the He/Ne laser, which badly affected the LS measurement, an optical filter was necessary to obtain UV light from the UV lamp. The light intensity at 254 nm was approximately $4.6 \text{ mW} \cdot \text{cm}^{-2}$ at the center of the test-tube.

Results and Discussion

Figure 2 shows UV irradiation time evolution of the light scattering intensity, $\langle I(q) \rangle_T$, of aqueous solutions containing $700 \times 10^{-3} \text{ M}$ of *N*-isopropyl acrylamide (NIPAm) monomers. The $\langle I(q) \rangle_T$ of the NIPAm solution with $50 \times 10^{-3} \text{ M}$ ammonium persulfate (APS) suddenly increased after UV irradiation for 3 min, followed by a strong fluctuation in $\langle I(q) \rangle_T$. This is a typical feature of a gelation/polymerization process.^[4,8] Indeed, the macroscopic gelation observed by the tube-tilting matched with the $\langle I(q) \rangle_T$ behavior. On the other hand, the NIPAm solutions without APS or UV irradiation did not show the increase in $\langle I(q) \rangle_T$ indicating that gelation/polymerization did not occur. This proved that the combination of APS and UV irradiation was important for inducing the gelation reaction.

In the same way, nearly 20 types of water-solvated monomers/polymers were investigated for gelation and classified into five categories as shown in Table 1. The ten monomers in category (A) of Table 1 have a $\text{CH}_2=\text{CHCO}-\text{R}$ monomer structure, where R represents various types of

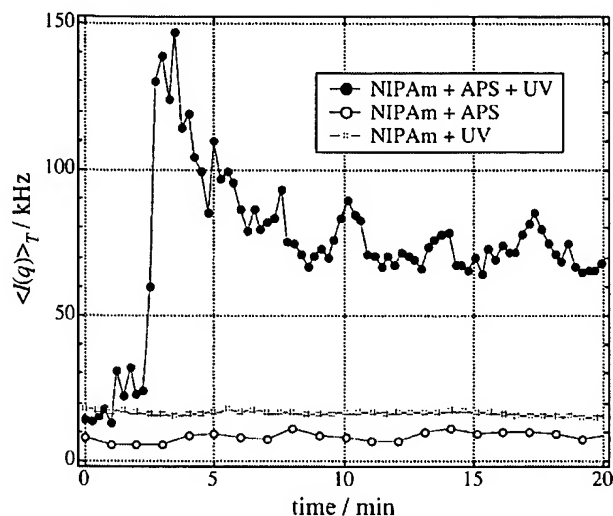
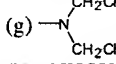
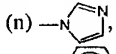
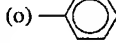


Figure 2. UV irradiation time evolution of $\langle I(q) \rangle_T$ for aqueous solutions containing 700×10^{-3} M of NIPAm monomer: (●) $C_{\text{APS}} = 50 \times 10^{-3}$ M with UV irradiation; (○) $C_{\text{APS}} = 50 \times 10^{-3}$ M without UV irradiation; (#) $C_{\text{APS}} = 0 \times 10^{-3}$ M without UV irradiation.

side chain, including acrylic acid (AAc), acrylamide, and NIPAm, which were well-known to undergo gelation by redox radical reaction using the cross-linker *N,N'*-methylenebisacrylamide (BIS).^[2–7] In our study, these ten types of monomer in aqueous solution easily changed into polymer gels by UV irradiation in the presence of APS without adding BIS. The gelation rate depended on the side-chain group and temperature. In the case of NIPAm solution, it took less than 5 min at 20 °C and a few minutes at 25 °C, as shown in Figure 2. The gelation of an AAc solution having a pK_a around 4.5 was found to be pH dependent. Indeed, it took more than 30 min for gelation at pH 7 instead of only 10 min at pH 3. It indicates that electrostatic repulsion between AAc monomers prevents them from coming in contact. The other monomers in category (A) were cross-linked at 20 °C in less than 30 min and the gels were transparent.

Next, we tested monomers having a $\text{CH}_2=\text{CH}-\text{R}$ structure (category (B) of Table 1). None of these underwent UV-induced gelation even after UV irradiation for more than 1 h. We therefore assumed that UV-induced gelation only applied to monomers having a $\text{CH}_2=\text{CHCO}-\text{R}$ structure, where R could represent a variety of functional groups.

Table 1. Classification of monomers and polymers investigated for the UV-induced gelation.

Monomer type	R group	Observed process
(A) $\text{CH}_2=\text{CHCO}-\text{R}$	(a) $-\text{OH}$, acrylic acid (b) $-\text{NHCH}(\text{CH}_3)_2$, <i>N</i> -isopropyl acrylamide (c) $-\text{N}(\text{CH}_3)_2$, <i>N,N'</i> -dimethyl acrylamide (d) $-\text{NH}_2$, acrylamide (e) $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, 2-(dimethylamino)ethyl acrylate (f) $-\text{O}(\text{CH}_2)_2\text{OH}$, 2-hydroxyethyl acrylate (g)  , 4-acryloyl morpholine (h) $-\text{NHCH}(\text{OH})\text{COOH} \cdot \text{H}_2\text{O}$, 2-acrylamidoglycolic acid monohydrate (i) $-\text{OCH}_2\text{CH}_2\text{OCOCH}_2\text{CH}_2\text{COOH}$, mono-2-(acryloyloxy)ethyl succinate (j) $-\text{NHC}(\text{CH}_3)_2\text{CH}_2\text{SO}_3$, 2-acrylamido-2-methylpropanesulfonic acid	gelled
(B) $\text{CH}_2=\text{CH}-\text{R}$	(k) $-\text{NHCOH}$, <i>N</i> -vinyl formamide (l) $-\text{CH}_2\text{COOH}$, vinyl acetic acid (m) $-\text{NHCOCH}_3$, <i>N</i> -vinyl acetamide (n)  , 1-vinyl imidazole (o)  , sodium <i>p</i> -styrenesulfonate	not gelled
(C) $\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}-\text{R}$	(p) $-\text{OH}$, methacrylic acid (q) $-\text{NH}_2$, methacrylamide	not gelled but polymerized
(D) $-(\text{CH}_2\text{CH}(\text{CO}-\text{R}))_n-$	(r) $-\text{OH}$, poly(acrylic acid) ($n = 100\,000$) (s) $-\text{NH}_2$, polyacrylamide ($n = 10\,000$)	gelled
(E) $\text{CH}_2=\text{CHCO}-\text{R}$	(t) $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{OSO}_3\text{CH}_3^-$, [2-(acryloyloxy)ethyl] trimethylammonium methylsulfate (u) $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, [2-(acryloyloxy)ethyl] trimethylammonium chloride (v) $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, (3-acrylamidopropyl) trimethylammonium chloride	not gelled

Category (C) monomers of Table 1 have $\text{CH}_2=\text{C}(\text{CH}_3)\text{-CO-R}$ structure, where the CH_3 group replaces H on the α -carbon. These monomer solutions did not undergo gelation. This is most likely because of the structural hindrance effect of two side-chain groups (CH_3 and CO-R) on the α -carbon, which may prevent cross-linking with another chain. The cross-linking mechanism in this UV-induced gelation has not been elucidated yet. However, as reported for the γ -ray radiation gelation of water-soluble polymers,^[24] we suppose that cross-linking between α -carbons occurs in addition to polyaddition at the chain end. Interestingly, category (C) monomers were not cross-linked but polymerized linearly. On the other hand, category (B) monomers have not even polymerized. Linear polymerization was confirmed by light scattering as will be further reported.

The UV-induced method was also effective for the gelation of aqueous solutions containing category (D) polymers (see Table 1). The cross-linking mechanism involved is likely to be the same as for the γ -ray radiation-induced cross-linking of polymers. This is quite different from redox or thermal radical reactions, where polymers do not react between each other even if cross-linkers are contained in the solution.

The results clearly indicate that the acryloyl structure ($\text{CH}_2=\text{CHCO-}$) plays an important role in the UV-induced gelation. In general, the combination of vinyl group ($\text{CH}_2=\text{CH-}$) and carbonyl group (C=O) in a monomer is known to form a conjugated structure, which increases the monomer reactivity with active radicals.^[12,31] This is likely to be the reason why such a unique UV-induced gelation takes place.

Here, we should mention some exceptions to UV-induced gelation. Category (E) monomers in Table 1 did not undergo gelation, though they had the $\text{CH}_2=\text{CHCO-R}$ structure. The reason is to be found in electrostatic interactions between side chains. These side chains are highly cationic in nature resulting in a strong electrostatic repulsion, which prohibits them from coming in close enough contact for cross-linking or polymerization to occur.

Though further investigations are necessary, this new technique of gel production opens a variety of industrial applications. In particular, it may be greatly useful to perform gelation without applying thermal and physical stimuli to a pre-gel solution in a closed system, for example, an emulsion droplet, or a fine pipe. Finally, it should be noted that the UV illuminance applied was slightly lower than usual because of the use of a UV filter for LS measurement. When full UV illuminance from the source was delivered (ca. $35 \text{ mW} \cdot \text{cm}^{-2}$), gelation occurred more quickly.

Conclusion

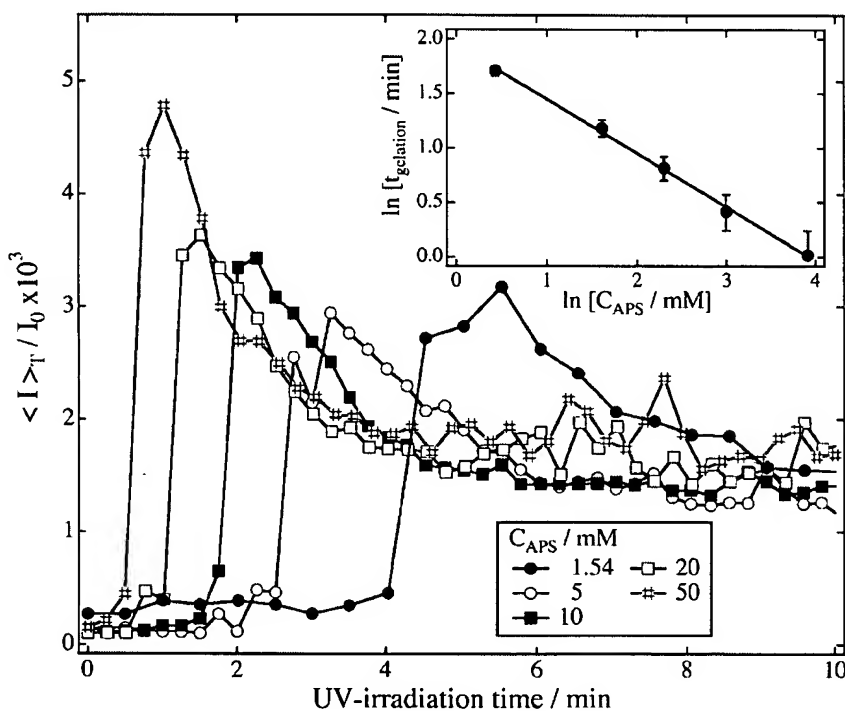
A novel method of producing polymer gels has been developed. For this method, persulfates were used as UV photoinitiators. The persulfate-containing aqueous acryloyl-type monomer/polymer solutions underwent gelation under UV irradiation. The method provides a number of advantages: (1) No cross-linkers are necessary. (2) No temperature control is required. (3) No additives, such as reaction accelerators and/or pH-adjustment agents, are required. (4) The photoinitiators used are transparent and nontoxic.

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Mechanism of UV-Induced Gelation of Acryloyl-Type Monomer and Polymer Solutions Using Persulfate as Photoinitiator

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An aqueous solution containing acryloyl-type monomers or polymers undergoes gelation by UV irradiation in the presence of APS as UV-photoinitiator. We investigate the mechanism of the UV-induced gelation using LS and ESR. In LS, the dependence of the gelation time t_{gelation} on the APS concentration C_{APS} is demonstrated for NIPAm solutions, and the relation between C_{APS} and t_{gelation} fits a power law function, i.e., $t_{\text{gelation}} \sim C_{\text{APS}}^{-1/2}$, indicating that UV-induced gelation progresses according to a radical polymerization mechanism. On the other hand, ESR data reveal that the UV-induced cross-linking reaction takes place at α -carbon atoms in acryloyl-type monomers and polymers.



Introduction

Chemically cross-linked polymer gels have been synthesized using various methods, such as low-temperature

redox,^[1–5] heat,^[1,6–9] high-energy electron beam,^[10–12] γ -ray,^[13–20] and UV.^[21–25] induced polymerizations. Heat-induced polymerization is a simple method in which heating to temperature higher than ca. 60 °C activates polymerization initiator to start chain reaction of monomers. However, when the polymer is very sensitive to temperature, e.g., the *N*-isopropylacrylamide (NIPAm) polymer,^[26] the method leads to net-prepared gel network with large structural inhomogeneities.^[27] Although low-

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temperature redox polymerization removes the temperature-sensitivity issue, it involves a more complicated procedure, e.g., adding an accelerator to a pre-gel solution to start the gelation reaction. Furthermore, when strictly size-limited emulsion droplets in an organic solvent are produced, the addition of accelerator solution may change the size of droplets or stirring process to help thorough mixing of the accelerator may destroy the droplets. Therefore, it can be said that photo-induced cross-linking is the most effective and convenient no-heating method to start a gelation reaction. However, high-electron beam- or γ -ray-induced polymerization is entailed by using too large irradiation device for self-handling in a small factory or research laboratory. As a result, UV-induced polymerization method would be the most useful and ideal method for daily-use as far as it produces gels having a variety of properties that compare with normal heat or redox synthesized polymer gels.

We have reported a novel method of producing polymer gels using UV irradiation.^[24,28] The gelation method involves the use of persulfate as UV-photoinitiator and successfully works with aqueous solutions containing acryloyl-type monomer ($\text{CH}_2=\text{CH}-\text{CO}-\text{R}$) or polymer ($-\text{[CH}_2=\text{CH}(\text{CO}-\text{R})]_n-$). It has an edge over the other gelation methods from the following points: (1) no cross-linker is necessary, (2) polymers are cross-linked with each other, i.e., monomers or polymers are directly cross-linked without requiring any cross-linking agent, (3) no temperature control is required, and (4) no additives, such as a reaction accelerator or pH-adjustment agent is required.

In this paper, we discuss the results of light scattering (LS) and electron spin resonance (ESR) investigations on UV-induced gelation process, i.e., how long it takes to get gelation, what kind of reaction happens, where cross-linking occurs, etc.

Experimental Part

Materials

N-Isopropylacrylamide (NIPAm), methacrylamide (MAM), and ammonium persulfate (APS) were purchased from Wako Chemical Co. Ltd., Tokyo. *N*-Vinylacetamide (NVAc) and poly(acrylamide) ($n = 10\,000$) (PAM) were from Aldrich Chemical Co., Inc.

Methods

UV Irradiation

UV irradiation was performed using a 500 W Deep-UV lamp (USHIO Inc., Tokyo,

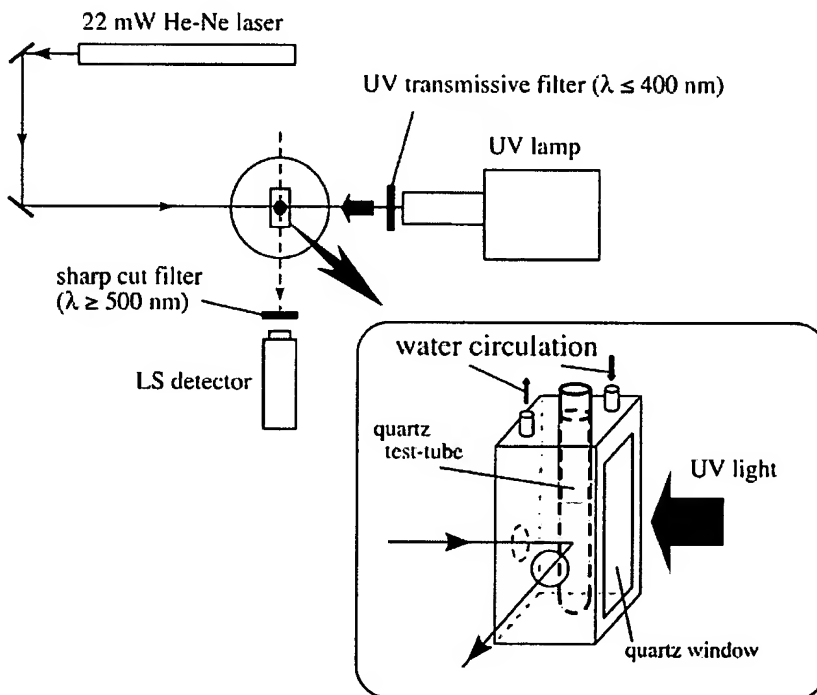
Japan) with an illuminance spectrum at $\lambda \leq 300$. APS was used as a UV-photoinitiator. APS has a strong absorption peak ranging 190–220 nm depending on C_{APS} . UV irradiation was applied to a pre-gel solution sample inside a quartz test tube with 8 mm in diameter. The light intensity at 254 nm was ca. $4.6 \text{ mW} \cdot \text{cm}^{-2}$ at the center of the test-tube. It should be noted that potassium and sodium persulfates have almost the same UV absorption spectra as APS and can also be used.

LS Intensity Measurements

Gelation and/or polymerization were monitored by scattered light intensity. It is known that gelation can be detected by a dramatic increase in scattered light intensity, $\langle I \rangle_T$, with large fluctuations. $\langle I \rangle_T$ was measured using a DLS/SLS-5000 (ALV, Co. Ltd., Langen, Germany) with a 22 mW He-Ne laser ($\lambda = 632.8 \text{ nm}$). Figure 1 shows the diagram of the gelation monitoring LS instrument with UV irradiation. He-Ne laser light came to the test-tube in a tube holder and $\langle I \rangle_T$ was detected at 90° . At the same time, the test-tube was irradiated by UV light on the opposite way from the incidence of He-Ne laser light. The temperature of the sample was controlled by thermostatic-water circulation in the tube holder. Since the light emitted by a UV lamp included some wavelengths as high as those emitted by He-Ne laser, which badly affected LS measurement, an optical filter was necessary to filter out inappropriate range of radiation from the UV lamp.

ESR

Electron spin resonance spectra of polymer solutions at each step of UV-induced polymerization in sealed ESR quartz tube were recorded on an ESP350E (Bruker) spectrometer at Toray Research



■ Figure 1. Experimental device for LS intensity monitoring.

Center, Inc. using an X-band (9.45 GHz) cavity, 100 kHz field modulation, with 5 G amplitude and 0.1 mW microwave power. Measurements were carried out at 20 K under UV irradiation.

Results and Discussion

Gelation Process

We observed the APS concentration (C_{APS}) dependence of the polymerization rate in order to know what kind of polymerization process was involved in the UV-induced gelation. Figure 2 shows UV irradiation time evolution of LS intensity, $\langle I \rangle_T$, of aqueous solutions containing 700×10^{-3} M of NIPAm at different C_{APS} . The longitudinal axis was divided by the intensity of incident radiation, I_0 , for normalization. NIPAm is one of the representative acryloyl-type monomers. The $\langle I \rangle_T$ of the NIPAm solution containing APS increased suddenly within 5 min of starting the UV irradiation depending on the C_{APS} which then went through large fluctuations. The sharp increase in $\langle I \rangle_T$ and/or the onset of large fluctuations of $\langle I \rangle_T$ is the typical features of gelation/polymerization process.^[2,6] Just around the peak of $\langle I \rangle_T$, the solution underwent gelation. The gelation time, t_{gelation} , became shorter with increasing C_{APS} . Indeed, the macroscopic gelation observed by the tube-tilting matched with the $\langle I \rangle_T$ behavior. It should be noted that, unlike the heat-induced or low temperature redox gelation, UV-induced gelation process

does not need cross-linkers. On the other hand, NIPAm solutions without APS did not show the increase in $\langle I \rangle_T$, indicating that gelation/polymerization did not occur.^[24] This fact clearly proves that the UV light did not directly impact monomers but APS, whereby free radicals are generated.

The inset in Figure 2 shows the double logarithmic plot of C_{APS} plotted versus t_{gelation} . Here, t_{gelation} includes experimental error up to ± 15 s due to time interval between measurements of $\langle I \rangle_T$. The relation between C_{APS} and t_{gelation} fitted a power law function well, i.e., $t_{\text{gelation}} \sim C_{\text{APS}}^{-1/2}$. In general, if a polymerization reaction is progressing through a radical mechanism, it is well known that polymerization time is proportional to the initiator concentration of the $-1/2^{\text{nd}}$ power.^[1] Thus the results showed that UV-induced gelation also progressed according to a radical polymerization mechanism in which APS was converted into a reaction inducer radical by UV irradiation. It also indicated that LS intensity measurement was an effective method to address kinetics study of such a polymerization.

Radical Generation

In order to know which part of the acryloyl-type monomer and polymer chain reacted using UV-induced gelation method, we did ESR measurements on four types of monomers and polymer, i.e., NIPAm, PAm ($-\text{[CH}_2-\text{CH}(\text{CO}-\text{NH}_2)]_n-$), NVAc ($\text{CH}_2=\text{CH}-\text{NH}-\text{COCH}_3$), and MAM ($\text{CH}_2=\text{C}(\text{CH}_3)-\text{CO}-\text{NH}_2$).^[24] NIPAm and PAm are the representative gelable acryloyl-type monomer and polymer, respectively. NVAc is an ungelable vinyl-type monomer, which does not have an acryloyl-type structure. MAM is a methacryloyl-type monomer, which readily polymerizes but is not gelable. The different behavior of those four samples during UV irradiation was observed by LS intensity measurements. Figure 3 shows UV irradiation time dependence of the four types of aqueous solution containing 0.700 M of monomer (or monomer unit for polymer) and 0.050 M of APS. NIPAm and PAm solutions underwent gelation under UV irradiation though gelation time depended on the type of monomer unit. Gelation was confirmed by a steep increase of $\langle I \rangle_T$ at ca. 1 min for NIPAm and onset of large fluctua-

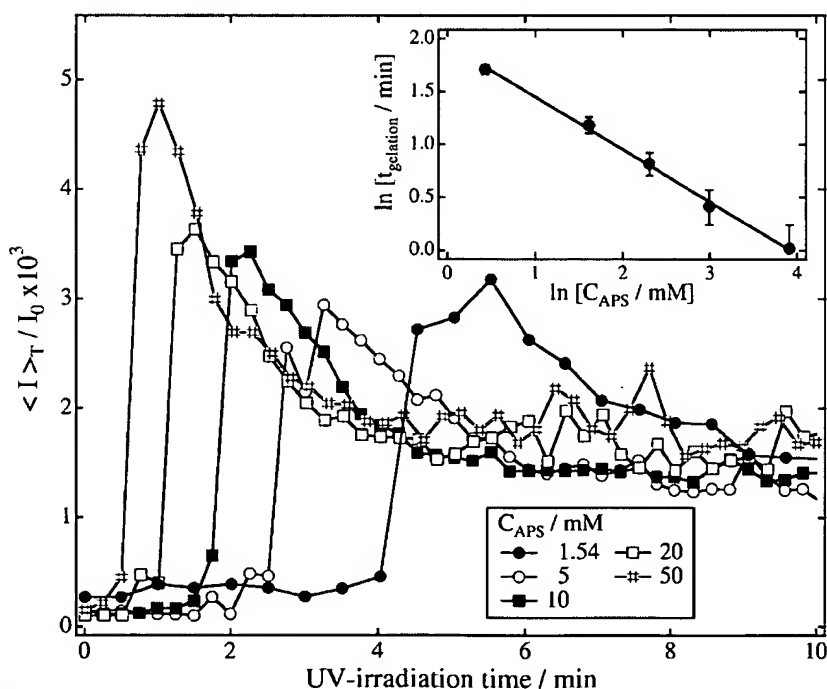


Figure 2. UV irradiation time dependence of LS intensity, $\langle I \rangle_T$, of pre-gel solutions containing 0.700 M of NIPAm and various amounts of APS. The inset shows a logarithmic plot of gelation time (t_{gelation}) versus initial APS concentration level (C_{APS}).

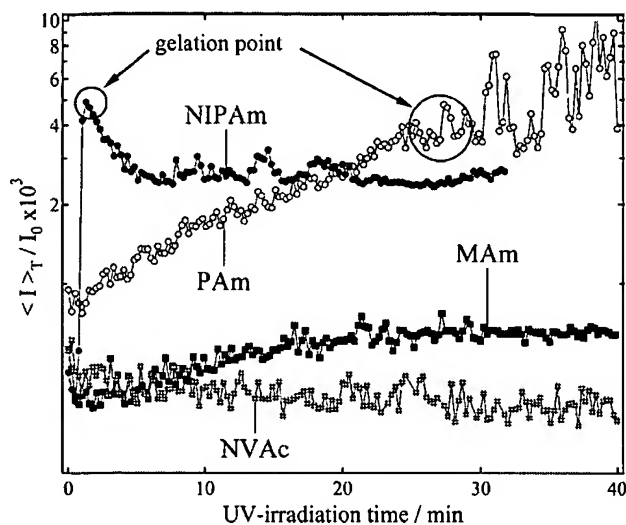


Figure 3. UV irradiation time dependence of LS intensity, $\langle I \rangle_T$, of pre-gel solutions containing 0.700 M of various types of monomer or polymer and 0.050 M of APS.

tions of $\langle I \rangle_T$ at ca. 27 min for PAm, respectively. On the other hand, in NVAc solution, $\langle I \rangle_T$ hardly changed under UV irradiation, indicating that no reaction was taking place. In MAm solution, $\langle I \rangle_T$ gradually increased during the first 15 min of UV irradiation, indicating that polymerization occurred.

ESR spectra were then recorded. Figure 4 shows ESR spectra at 24 min, after starting UV irradiation and the spectrum-simulations. In Figure 4(a), an ESR spectrum of NIPAm are shown, which has five peak signals, shown by small arrows in the figure. This spectrum was well reproduced with a spectrum-simulation corresponding to a $-\text{CH}_2-\dot{\text{C}}^*(\text{R})-\text{CH}_2-$ structure, where an active radical was generated on the α carbon atom. This α carbon atom with the active radical was estimated to form a new cross-linking point with another polymer chain. Figure 4(b) shows the ESR spectrum of PAm, which was separated into two characteristic spectra by simulation. One was of similar type as the NIPAm spectrum showing cross-linkable parts. This supports the fact that both aqueous solutions undergo gelation without cross-linker. The other spectrum exhibits one sharp derivation peak related to a $-\text{CH}_2-\dot{\text{C}}^*(\text{R})-(\text{CH}=\text{CR})_n-\text{CH}_2-$ structure. It gives evidence of unlocalized radicals that are not involved in cross-linkage formation. Figure 4(c) shows the ESR spectrum of ungelable NVAc monomer. This spectrum could also be separated into two spectra. One has four sharp peaks relating to methyl radicals. The other one is very similar to the $-\text{CH}_2-\dot{\text{C}}^*(\text{R})-\text{CH}_2-$ structure observed in Figure 4(a) and 4(b). However, when looking closer, it emerges that the width of each peak is narrower in Figure 4(c) than in Figure 4(a) and 4(b), as shown by dotted lines in the simulation spectra. This strongly suggests that

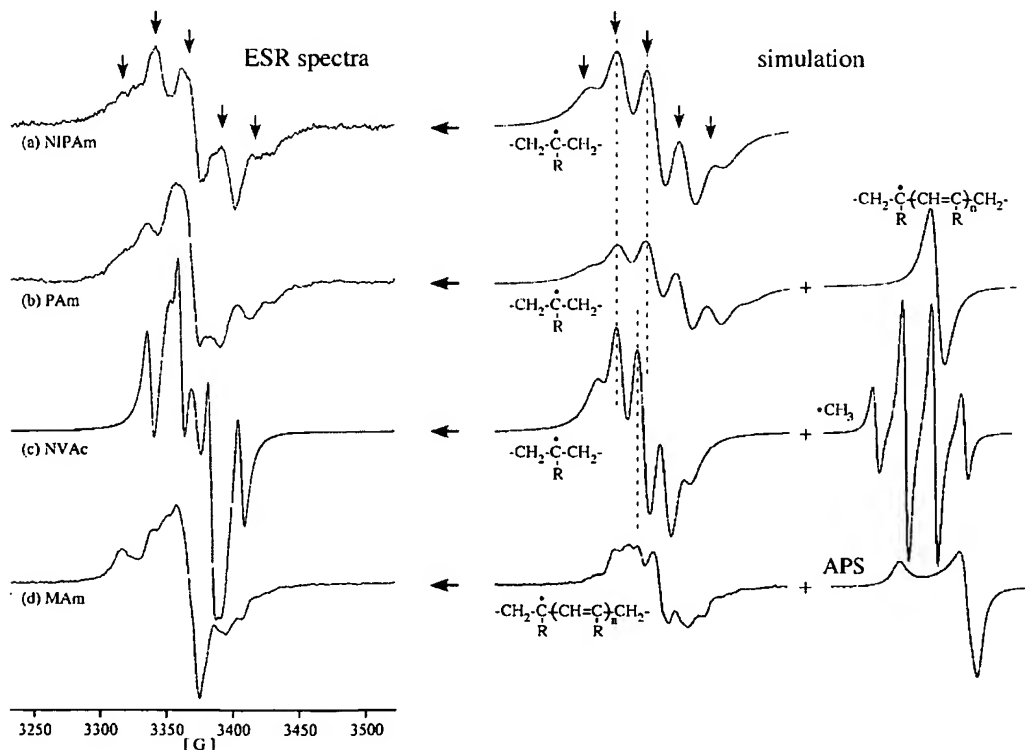


Figure 4. ESR spectra of various types of monomer and polymer: (a) NIPAm, (b) PAm, (c) NVAc, and (d) MAM. The right-hand side of thick arrows shows the results of spectrum-simulation for ESR spectra observed.

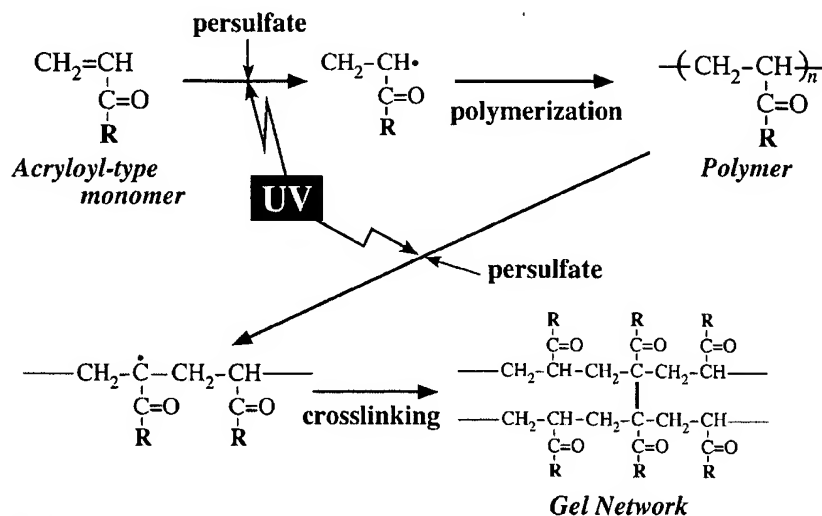
the monomer is not polymerized. It raises the issue of the reason why NVAc monomers did not polymerize even though the $-\text{CH}_2-\text{C}^*(\text{R})-\text{CH}_2-$ radical structure was produced. It is likely to result from the nature of the R component. When R is $-\text{NHCOCH}_3$, the α carbon atom is not linked to $\text{C}=\text{O}$, in consequence of which a free radical on the α carbon atom is easily drawn to the amide group. The reactivity of the α carbon atom was therefore impaired, resulting in a failure to polymerize. The ESR spectrum of an MAM solution is shown in Figure 4(d). It was also separated into two spectra corresponding to an unreacted APS free radical and to unlocalized radical structure, respectively. As shown in Figure 3, MAM solutions did not undergo gelation but polymerization. In this case chain no branching could occur, implying that the $-\text{CH}_2-\text{C}^*(\text{R})-\text{CH}_2-$ radical was not generated. Therefore, the result in Figure 4(d) looks reasonable.

Gelation Mechanism

Based on ESR results, a UV-induced gelation process is proposed in Figure 5. First, in the presence of persulfate, UV irradiation generates a free radical on the α carbon atom of the acryloyl-type monomer, inducing polymer formation along the main chain direction. Next, further radical generation occurs on the α carbon atom of the polymerized monomer connection. Then, this radical forms a cross-link with an activated α carbon atom of another polymer chain, resulting in gelation of the entire solution. It should be noted that we do not yet confirm whether a direct bond between the α carbon atoms of different polymers was formed or whether a polymer chain exists between those α carbon atoms. The fact that cross-linking and gelation occur not only in monomer solutions but also in polymer solutions is one of the remarkable features of the UV-cross-linking gelation method described here.

Conclusion

In order to understand the new gelation method, which enables us to produce polymer gels from acryloyl-type monomer or polymer solution using UV irradiation in the presence of persulfate as photoinitiator, the gelation mechanism was investigated using LS intensity and ESR measurements. LS intensity monitoring showed that the UV-induced gelation time was inversely proportional to the square root of the level of persulfate, i.e., UV-photoinitiator, indicating that gelation progresses according to a radical



■ Figure 5. Diagram of the UV-induced gelation process.

polymerization process. ESR measurements confirmed that a free radical was generated on the α carbon atom of the acryloyl-type monomer or polymer. The UV-induced gelation was estimated to occur through cross-linking between the activated α carbon atoms of the polymers.

Acknowledgements: We are grateful to Dr. Yoji Yamaguchi, Toray Research Center, for his support in performing the ESR measurements.

Received: September 7, 2006; Revised: October 27, 2006;
Accepted: October 30, 2006; DOI: 10.1002/macp.200600460

Keywords: acryloyl group; electron spin resonance; gelation; light scattering; persulfate; UV irradiation

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